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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/571,802	12/13/1995	DOUGLAS N. ISHII		3216

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EXAMINER	
PAK, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/571,802	ISHII, DOUGLAS N.	
	Examiner	Art Unit	
	Michael Pak	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☒ This action is **FINAL**. (FROM) 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-20-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on June 20, 2005 has been entered.

Response to Amendment

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office actions.

3. Applicant's arguments filed 20 June 2005, have been fully considered but they are not found persuasive.

4. The Declaration of Ishii under 37 CFR 1.132 filed 5 November 1998 (Paper No. 16) remains insufficient to overcome the rejection of claims 24-71 based upon 35 U.S.C. 112, first paragraph because the Declaration is unsigned. The submission of the signed Declaration will overcome the this objection.

Claim Rejections - 35 USC § 112

5. Claims 24-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description and new matter rejection.

Claims 24-71 recite the terms "IGF-I" and "IGF-II" which encompass proteins which are allelic variants given the definition of "IGF-I" and "IGF-II" on pages 5-6 of the specification. Thus, the claims encompass a subgenus of "naturally occurring allelic variants" which is not disclosed in the specification. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutation sites (see Rieger et al., *Glossary of Genetics* (1991), pages 16-17). However, the specification only discloses by name one species each of IGF-I and IGF-II in the working example. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim. *University of California v. Eli Lilly and Co.*

(CAFC) 43 USPQ2d 1398 held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification.

Claims 24-71 recite the terms "parenteral nonintracranial administration" which are not disclosed in the specification. The original claims recite parenteral administration that is generic and does not provide support for the subgeneric limitation claimed. The specification does not provide written descriptive support for the subgenus encompassing administration by all means other than intracranial.

Applicants argue on pages 3-4 that IGF claim limitation does not include derivatives of IGF's including fragments of IGF's, analogs of IGF's, or analogs of fragments of IGF's because of the definitions of IGF-I and IGF-II in the specification on page 5. However, the specification on page 5, lines 21-25 specifically recite that "IGF-I also encompasses ... IGF molecules with substantial sequence homology to human and animal IGF-I that bind to type I IGF receptors." Thus, the claims encompass and claim a subgenus of "naturally occurring allelic variants" which is not disclosed in the specification. The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutation sites (see Rieger et al., *Glossary of Genetics* (1991), pages 16-17). However, the specification only discloses by name one species each of IGF-I and IGF-II in the working example. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of

alleles is such that they are variant structures and in the present state of the art the structure of one does not provide guidance for the structure of others. Appellant does not describe a representative number of the claimed genus, and the common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim. *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification.

Applicants discuss on page 5 of the Brief a newly submitted reference "Concise Encyclopedia Biochemistry" which has not been considered because it does not comply with 37 CFR 1.195.

Applicants on page 5 of the Brief argue that *Eli Lilly* does not apply because the specification describes and defines IGF's and persons of skill in the art understand the functional and structural characteristics of IGFs. However, the issue is whether applicant's definition in the specification on page 5, lines 21-25 when it specifically recites that "IGF-I also encompasses ... IGF molecules with substantial sequence homology to human and animal IGF-I that bind to type I IGF receptors" encompasses generically IGF molecules other than the species disclosed in the specification. The definition on page 5 encompasses a generic class of IGF-I while the specification discloses only the species of IGF-1. Eli Lilly does prohibit claiming a genus when the genus of molecules cannot be envisioned from the disclosed species. Applicants'

citation of *Amgen Inc. v. Hoescht Marion Roussel, Inc.* does not overcome the rejection because unlike *Amgen* the inability to envision the generic sequences of IGF-I or IGF-II when only the species are provided in this application is pertinent to *Eli Lilly.*

Applicants argue on page 4 of the Brief that the rejection is not correct regarding the new matter rejection of claims 24-71 which claims now encompass the terms "IGF-I consists essentially of an amino acid sequence of a naturally occurring IGF-I" and "IGF-II consists essentially of an amino acid sequence of a naturally occurring IGF-II" are not persuasive because the claim limitations are not disclosed in the specification,. Pages 5-6 of the specification define the terms "IGF-I" and "IGF-II" that are generic and does not provide support for the subgeneric limitations claimed. Applicants argue that "naturally occurring" IGFs is not new matter because a persons skilled in the art would understand that functional derivatives of IGF's are not naturally occurring IGF's However, the specification on page 5, lines 21-25 specifically recite that "IGF-I also encompasses ... IGF molecules with substantial sequence homology to human and animal IGF-I that bind to type I IGF receptors." Thus, claims encompass "IGF-I" and "IGF-II" which are generic and does not provide support for the subgeneric limitations claimed. Applicants argue that the claims only encompass all naturally occurring forms of IGFs. However, the definition in the specification is generic to the subgeneric claim limitation of "naturally occurring" and the specification does not disclose "naturally occurring." Furthermore, the specification does not disclose what is non-naturally occurring or not naturally occurring which is necessary to disclose the IGFs that are naturally occurring.

Applicants argue in the page 6 of the Brief that the term "parenteral nonintracranial administration" is not new matter. Applicants argue that the specification disclose examples of "parenteral nonintracranial administration." However, while the specification discloses the genus of "parenteral administration" , it does not disclose the subgeneric limitation of "nonintracranial". The specification does not disclose the negative limitation of "nonintracranial" and does not disclose the exclusion of intracranial from the genus of "parenteral administration" the intracranial to create a new subgenus of "parenteral nonintracranial administration" which is not disclosed in the specification. Applicants argue that thespecification on page 3 discuss that intracranial administration was invasive and difficult, risky and required costly surgical procedure. However, the specification does not exclude intracranial from the parenteral administration method. The discussion of blood brain barrier does not support "parenteral nonintracranial administration" but rather supports "parenteral administration."

6. Claims 24-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of parenteral administration of species of IGF-I, IGF-II, or a combination of both IGF-I and II for the treatment of locus ceruleus noradrenergic neurons ablation by 6-hydroxydopamine, does not reasonably provide the full scope of enablement for parenteral administration of IGF-I or IGF-II, for traumatic injury of the central nervous system (CNS) or spinal cord and treating stroke. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons set forth in the past office actions.

The terms "traumatic injury to the central nervous system" encompass a physical or mental injury to the central nervous system (see Stedman's Medical Dictionary(U)). Thus, claims 24-33 encompass any physical or mental injury to the CNS. The term "stroke" encompasses both ischemic or hemorrhagic lesions. Thus, claims 34-45 encompass treatment for all types of stroke. The terms "traumatic brain injury" encompass a physical or mental injury to the brain (see Stedman's Medical Dictionary(U)). Thus, claims 40-45 encompass any physical or mental injury to the brain. Claims 57-71 recite and encompass the term "injury to the central nervous system" which encompasses any physical or mental injury to the central nervous system. .However, the specification fails to teach treating the generic injury or stroke. The claims generic encompass dysfunction in the CNS from molecular, cellular, physiological, neural network, to behavior in normal and disordered state and the state of the art at the time of the invention provides no reference to indicate that administering IGF-I or -II will treat all such injuries in the CNS or spinal cord. Just a few examples of such injury includes schizophrenia, depression, spinal cord transection, ion channel modulation, or memory which the state of the art is silent with respect to treatment with IGF-I or II. Baringa (A34) provides the state of the art after the time of the invention where treatments of nervous system diseases with neurotrophic factors are unpredictable and that treatment of any one disease is not predictive of another. Baringa further indicates that although treating peripheral neuropathy may be more

promising, even with sensory peripheral neuropathy, there is a difference between diabetic neuropathy and cancer chemotherapy induced neuropathy (A34, page 774, left column). Thus, the treatment of a nervous system disease is an unpredictable art where one model of treatment for neuropathy is not predictive of the another model of treatment. Although the specification provides working examples of IGF-II mRNA changes in the streptozotocin induced diabetic rat brain by administration of IGF-I (pages 11-12) and working examples of IGF-II administration for treatment of 6-hydroxydopamine (6OHDA) induced noradrenergic locus ceruleus ablation by measuring limb withdrawal reflex, such examples are not predictive of effecting any changes in CNS or spinal cord, or treating any disorders or diseases in the brain or spinal cord, because the state of the art indicates that any one model of treatment for a disease is not predictive of the another model of treatment. Further indication that treatment of neurological disease is an unpredictable art is indicated by Jackowski(R) who teaches that neurons do not regenerate the CNS because CNS environment is non-supportive or actively inhibitory to neuronal regeneration (reference R is cited as being of interest to applicant's specification, page 305, right column, bottom paragraph). Working example in the specification of IGF-II administration for treatment of 6-hydroxydopamine (6OHDA) induced noradrenergic locus ceruleus ablation by measuring limb withdrawal reflex is not predictive of treating any disorders or diseases in the brain or spinal cord, because the state of the art indicates that CNS is inhibitory to neuronal regeneration and regeneration is necessary for treatment of CNS diseases. Shepherd(S) disclose the state of the art by teaching how the CNS is categorized and

the noradrenergic neurons of the locus ceruleus is but a small region in the whole CNS and the noradrenergic neurons of the locus ceruleus are different from other regions of the brain such as the dopaminergic neurons of the striatum(reference S is cited as being of interest to applicant's specification, page 499, figure 24.9 and section "Norepinephrine"; page 501, figure 24.10 and left column). Since the treatment of CNS is an unpredictable art because the CNS is inhibitory to regeneration, the working example for treatment of noradrenergic locus ceruleus is not predictive of any other regions of the brain nor any other types of neurons. Finally, the treatment of CNS injury encompasses treatment of AIDS dementia which is an unpredictable art because the state of the art at the time of the invention does not indicate any reference that administering IGF-I or -II will be effective in treatment of AIDS dementia. Barnes(T) teaches the state of the art at the time of the invention regarding how AIDS virus injures the nervous system and indicates uncertainty and controversy about the mechanism of the injury (S, page 1574, left column, top paragraph). Barne's discussion concerning AIDS dementia is limited to the etiology and no discussion concerning treatment with IGF-I or II is provided (S, page 1574, left column, top paragraph). The working examples are not predictive of treating AIDS dementia because the specification fails to provide a model for AIDS dementia which could be used predict the effect of treatment by administering IGF-I or -II. Without such guidance, the determination of IGF-I or -II effect on treating AIDS dementia requires empirical experimentation and are not predictive of treating AIDS dementia. Thus without further guidance, it would require undue experimentation to determine all the changes effected in the CNS or spinal cord

by administering IGF- or IGF-II as well as all the disorders of the brain or spinal cord including AIDS dementia. Furthermore, the specification fails to teach the treatment for the full scope of stroke diseases. The state of the art is silent with respect to using IGF to treat stroke (see Berkow et al.(V)). The treatments are related to using anticoagulants or treating atherosclerosis or hypertension, but not using IGF. Furthermore, the specification fails to make a nexus from the model of using IGF-I and II for the treatment of locus ceruleus noradrenergic neurons ablation by 6-hydroxydopamine to treating stroke or Parkinson disease. Without such guidance, the determination of IGF-I or -II effect on treating the full scope of stroke diseases is unpredictable because strokes can occur in other regions of the brain and there is no relationship between the noradrenergic neuronal ablation by 6-hydroxydopamine of locus ceruleus. Thus without further guidance, it would require undue experimentation to treat stroke by administering IGF- or IGF-II.

Upon further consideration, the Declaration of Ishii filed 16 November 1998 is not found persuasive to overcome the enablement rejection.

Appellant argues that the post-filing date evidence clearly demonstrates the operativeness of the methods in a mammal as taught and claimed. However, appellant has failed to make a nexus from the model in the specification of using IGF-I and II for the treatment of locus ceruleus noradrenergic neurons ablation by 6-hydroxydopamine to treating stroke, traumatic injury to the CNS or the brain. Furthermore, the specification fails to teach the methods of administration of IGF which results in

successful treatment an established model for diseases of stroke or traumatic injury to the brain or CNS.

Claim Rejections - 35 USC § 102

7. Claims 24-71 are rejected under 35 U.S.C. 102(e) as being anticipated by Lewis et al.(A1).

The terms "traumatic injury to the central nervous system" or "traumatic brain injury" encompass a physical or mental injury to the central nervous system or brain. Lewis et al. teach a method of treating injury and stroke (column 4, lines 1-22). Lewis et al. teach a method of parenteral administration of IGF-I or IGF-II with specific dosage ranges of 1ug/kg/day to 1 g/kg/day as well as ranges 0.01 mg/kg/day to 100mg/kg/day (column 10, lines 3-22). Furthermore, IGF I and II inherently cross the blood brain barrier.

Claims 46-56 encompass a method of treating locus ceruleus neurons with IGFs. Lewis et al. teach method of treatment for diseases such as Alzheimer's disease, stroke, epilepsy, amyotrophic lateral sclerosis, or Parkinson's disease by administering an effective amount of IGF I or IGF II or a combination thereof. Diseases such as stroke and Parkinson's disease affect the locus ceruleus neurons. Thus, the treatment by the parenteral administration of IGF I or IGF II to treat these diseases comprise a nonintracranial administration of an IGF in an amount to effective to treat the locus ceruleus neurons.

Claims 57-67 encompass a method of treating the central nervous system. Lewis et al. teach method of treatment for diseases such as Alzheimer's disease, stroke, epilepsy, amyotrophic lateral sclerosis, or Parkinson's disease by administering an effective amount of IGF I or IGF II or a combination thereof. These diseases are injury which affect the central nervous system.

Claims 68-71 are dependent claims that encompass a method of treating with IGF damage to locus ceruleus associated with Parkinson's disease. Parkinson's disease is associated with damage to the locus ceruleus neurons. Thus, the treatment by the parenteral administration of IGF I or IGF II to treat Parkinson's disease comprise a nonintracranial administration of an IGF in an amount effective to treat the disease, wherein the locus ceruleus is damaged.

Applicants argue that Lewis et al. does not teach treatment of the brain by parenteral nonintracranial administration. Applicants argue that Lewis et al. teaches away from parenteral nonintracranial administration. However, Lewis et al. teach the method of parenteral administration of IGF-I or IGF-II with specific dosage ranges of 1ug/kg/day to 1 g/kg/day as well as ranges 0.01 mg/kg/day to 100mg/kg/day (column 10, lines 3-22). Lewis et al. teach different modes of parenteral administration of the IGF-1 and IGF-II, such as intravenous, subcutaneous, intramuscular and many more (column 9, lines 18-30) which are not intracranial. Furthermore, IGF I and II inherently cross the blood brain barrier. Lewis et al. teach solution of IGF acting across the blood-brain by making the polypeptide more lipophilic, by conjugating the polypeptide of interest to a molecule which is naturally transported across the barrier or by reducing

the overall length of the polypeptide chain (column 3, lines 39-60; column 5, lines 10-26; column 6, lines 50-68; column 8, lines 45-55; and column 9).

Applicants argue that the Examples of Lewis are limited to either in vitro experiments or administration of modified IGF to rat models via a hole in the skull. However, Lewis et al. teach the method of parenteral administration of IGF-I or IGF-II with specific dosage ranges of 1ug/kg/day to 1 g/kg/day as well as ranges 0.01 mg/kg/day to 100mg/kg/day (column 10, lines 3-22). The Lewis et al. patent is not limited to the working example but also includes summary of the invention that includes the use of the peptides in parenteral administration of IGF-I and IGF-II (columns 9-10). Lewis et al. teach different modes of parenteral administration of the IGF-1 and IGF-II, such as intravenous, subcutaneous, intramuscular and many more (column 9, lines 18-30) which are not intracranial.

Applicants argue that the scope of the IGF in applicants claims does not include the "functional derivatives" of Lewis et al. However, the definition in the specification on page 5, lines 21-25 specifically recites that "IGF-I also encompasses ... IGF molecules with substantial sequence homology to human and animal IGF-I that bind to type I IGF receptors." Thus the IGF encompasses generically IGF molecules other than the species disclosed in the specification. Furthermore, the definition does not exclude fragments or derivatives.

8. No claims are allowed.

9. This is a RCE continuation of applicant's earlier Application No. 08/571,802. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Pak whose telephone number is (703) 305-7038. The examiner can normally be reached on Monday-Friday from 8:30 to 2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Michael D. Pak
Primary Patent Examiner
Art Unit 1646
1 September 2005